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Masahiko Okada

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER

SCHUBERG, LAURA J

ART UNIT

PAPER NUMBER

1657

NOTIFICATION DATE

DELIVERY MODE

09/18/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 04/02/2009 and 05/08/2009 have been entered.

On 04/02/2009, claims 1, 4-11, 13, 14, 17-24, 38 and 39 were pending. Claims 1, 4-7, 10, 13, 14, 17-24 were amended. Claims 38 and 39 were newly added. Claims 2, 3, 12, 15, 16, 26-37 were newly canceled.

On 05/08/2009, claim 1 was amended and no claims were newly added or canceled.

Currently claims 1, 4-11, 13, 14, 17-24, 38 and 39 are pending.

Claims 1, 4-11 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/23/2007.

Claims 13, 14, 17-24, 38 and 39 have been considered on the merits.

Applicant is requested to note that the Examiner for this application has changed. Future correspondence should be directed to Laura Schuberg, Art Unit 1657, whose contact information can be found below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 14, 17-24, 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al in view of Miyauchi et al (EP 1148142 A1, as cited in the IDS filed 21 January 2005) Matsui et al (US 6,194,164).

A kit for selective measurement of triglycerides contained in very low density lipoprotein and intermediate density lipoprotein or in very low density lipoprotein in a test sample is claimed comprising two reagents.

Okada et al teach a reagent comprising a reaction promoting agent (i.e., a selective reaction promoter) that can be a surface-active agent such as a polyoxyalkylene or a derivative thereof, including polyoxyethylene alkyl ether and polyoxyethylene alkyl phenyl ether (i.e., polyoxyalkylene straight-chain alkyl ethers). Okada et al teach that the reaction promoting agent interacts with lipoprotein lipase to eliminate triglycerides in lipoproteins other than very low density lipoproteins and intermediate density lipoproteins (i.e., VLDL and IDL) by carrying out a series of reactions which make hydrogen peroxide or reduced coenzyme. Okada et al teach that the enzymes used for decomposition of triglycerides into hydrogen peroxide for measurement include lipoprotein lipase, which gives glycerol, which is then changed to glycerol 3-phosphate by glycerol kinase, that changes into dihydroxyacetone-3-phosphate by glycerol-3-phosphate oxidase, followed by colored assay of the generated

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hydrogen peroxide. Also, Okada et al teach that glycerol-3-phosphate dehydrogenase can be used in lieu of glycerol-3-phosphate oxidase to produce NADH so that NADH can be measured (see, for example, Detailed Description section). Okada et al teach a first reagent comprising a reaction promoting agent and enzymes including lipoprotein lipase as well as other enzymes to produce either hydrogen peroxide or a reduced coenzyme, which eliminates the triglycerides from the lipoproteins other than the VLDL's and the IDL's, which includes those from LDL's and HDL's. Okada et al also teach a second reagent which then quantifies the triglycerides in the VLDL's and the IDL's, comprising a reaction promoting agent and enzymes (i.e., lipoprotein lipase) which can react with the triglycerides to generate either hydrogen peroxide or a reduced coenzyme, wherein the reaction promoting agent can be a polyoxyalkylene or a derivative thereof, including polyoxyethylene alkyl ether and polyoxyethylene alkyl phenyl ether. Furthermore, Okada et al teach that the reagents may also contain reaction "auxiliary substances" (i.e., reaction assistants) which can assist the reaction promoter agents, examples of which include polyanion, halogen ion, and metal ions (see, for example, Detailed Description section). Addition of auxiliary substances for the promotion of selectivity is also taught to be desirable as well (pages 5-6).

While Okada et al do not specifically package the claimed reagents into a kit with the claimed ratio of polyoxyalkylene in its ether or ester compound, use of a kit containing reagents is suggested as acceptable (page 36).

Miyauchi et al beneficially teach reagents for quantitating triglycerides (TG) in lipoproteins, providing a reagent for allowing the reaction of lipoproteins other than the

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particular lipoprotein, as well as providing lipoprotein lipase (LPL), glycerol kinase (GK), glycerol-3-phosphate oxidase (GPO), and peroxidase. Miyauchi et al suggest that these reagents are suitable for quantitative analysis (page 3 paragraphs 20-21) and include the form of a kit in which the reagents are divided into two or more parts depending on their components (page 3 paragraph 22). Furthermore, Miyauchi et al beneficially teach that it is useful to add a surfactant or to add an enzyme while allows reaction of a particular lipoprotein (see, for example, page 3 and page 4). Miyauchi et al beneficially teach that in measuring TG in particular lipoproteins, it is preferable to add a reagent for eliminating the reaction of lipoproteins other than the lipoprotein of interest, such as a surfactant which would allows LPL to react specifically with particular lipoproteins, so that a precise measurement of TG in a particular lipoprotein of interest can be made. Subsequently, Miyauchi et al teach that the same sample can then have a second reagent added to it which contains a surfactant that allows reaction of the particular lipoprotein of interest as well as LPL, so as to obtain a measurement of TG in the lipoprotein of interest.

Matsui et al beneficially teach that preferred surfactants which act on lipoproteins other than LDL include polyoxyalkylene oxide derivatives having HLB (i.e., hydrophilic-lipophilic balance) values of not less than 13 and not more than 15. Matsui et al teach that one particular example is polyoxyethylene nonylphenyl ether (see, for example, col. 3, line 35). Matsui et al further teach that surfactants which act on all lipoproteins include polyoxyalkylene oxide derivatives having HLB values of not less than 11 and not more than 13, particularly polyoxyethylene nonylphenyl ether, for example (see, for

example, col. 4, lines 10-40). Matsui et al beneficially teach that the method for calculating HLB of surfactants is well-known in the art, a method which is based in part upon the molecular weight of the hydrophilic portion of the surfactant (e.g., polyoxyethylene). Different concentration ranges for surfactants are taught for the first step (column 3 lines 53-55) and the second step (column 5 lines 18-20) of the quantitating method and these ranges would allow for a ratio of surfactants that would include 1.1 or 1.2 as claimed by Applicant.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the reagent mixtures disclosed by Okada et al based upon the beneficial teachings provided by Miyauchi et al, with respect to the art-recognized method for using a two-step process using different reagents containing surfactants and LPL to determine TG in lipoproteins, and by Matsui et al, with respect to the art-recognized method of using surfactants of a particular HLB value or molecular weight to solubilize specific lipoproteins, as discussed above. Okada et al specifically teach reagents which act on lipoproteins using surfactants that are derivatives of polyoxyalkylene and lipoprotein lipase so as to generate either hydrogen peroxide or reduced coenzyme to determine the amount of triglyceride in VLDL and IDL. Furthermore, Matsui et al particularly point out that polyoxyethylene nonylphenyl ether is one specific polyoxyalkylene derivative that is a preferred surfactant for acting on lipoproteins, and that the HLB value of a surfactant is important in determining its specificity toward lipoproteins. Matsui et al further beneficially teach that particular HLB values of surfactant are beneficial for acting on particular lipoproteins, and that

calculating HLB values is well known in the art, and therefore, it would have been both obvious and beneficial for one of skill in the art at the time the claimed invention was made to use particular surfactants, as described by both Okada et al and Matsui et al, in particular mole number ratios of the polyoxyalkylene derivatives (i.e., the hydrophilic group) so as to vary the selectivity of the surfactant for different lipoproteins based upon the HBL value, as beneficially taught by Matsui et al. The result-effective adjustment of particular conventional working conditions (e.g., using a particular surfactant and/or using a particular ratio of added polyoxyalkylene in each of the selective reaction promoters) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. Clearly all of the claimed ingredients are known in the art to be suitable for use together in methods for quantitating triglycerides in lipoproteins and would thus be obvious for one of ordinary skill in the art to package them as kits. It is well-known in the art to separately package ingredients to be combined together for the known advantage of improved storage and prevention of premature reaction.

In addition, as far as the inclusion of written instructions in the kit, M.P.E.P. § 2112.01 recites, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art." See *In re Ngai* and *In re Gulack* (citations omitted).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 04/02/2009 have been fully considered but they are not persuasive.

Applicant argues that the combination of the Okada et al, Miyauchi et al and Matsui et al do not describe or suggest using different lipases having different activities in two different reagents and selecting a specific molar ratio of the selective reagents. Applicant points to specific working examples in the references to demonstrate that the inclusion of 2 different lipases are not taught by the references.

This is not found persuasive because the teachings of the references are not limited to the working examples that they provide. Okada et al specifically teaches that one of ordinary skill in the art may make an alternative reaction promoting agent by combining two or more kinds of ingredients and suggests modifying the concentrations, content and specifically the enzymes used (page 35 of the translation). Clearly Okada et al suggest that these ingredients may be used in different combinations and separated into two reagents for use in the method.

Applicant argues that Matsui et al do not teach adjusting HLB values so as surfactants act on different lipoproteins and different lipoprotein lipases, or adjusting a ratio of the average moles of polyoxyalkylene in its ether or ester compound. Applicant asserts that the HLB value reflects a degree to which a surfactant is hydrophilic or

lipophilic and does not show how many moles of a surfactant is added or ratio of surfactants in two steps.

This is not found persuasive because Matsui et al teach that the method for calculating HLB of surfactants is well-known in the art, a method which is based in part upon the molecular weight of the hydrophilic portion of the surfactant (e.g., polyoxyethylene). Also, different concentration ranges for surfactants are taught for the first step (column 3 lines 53-55) and the second step (column 5 lines 18-20) of the quantitating method and these ranges would allow for a ratio of surfactants that would include 1.1 or 1.2 as claimed by Applicant. Clearly the use of surfactants in the same ratio as claimed by Applicant is known in the art.

Applicant argues that the methods and reagents of Okada et al, Miyauchi et al and Matsui et al are different from each other because they use different enzymes, measure different substances and exhibit different behaviors towards surfactants such as polyalkylene derivatives. Applicant asserts that it would not have been obvious what surfactants and HLB values to select based on the contradictory data of Okada et al and Matsui et al for the selective measurement of TG in VLDL and IDL.

This is not found persuasive as the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Okada et al specifically teach reagents which act on lipoproteins using surfactants that are derivatives of polyoxyalkylene and lipoprotein lipase so as to generate either hydrogen peroxide or reduced coenzyme to determine the amount of triglyceride in VLDL and IDL. Furthermore, Matsui et al particularly point out that polyoxyethylene nonylphenyl ether is one specific polyoxyalkylene derivative that is a preferred surfactant for acting on lipoproteins, and that the HLB value of a surfactant is important in determining its specificity toward lipoproteins. Clearly one of ordinary skill in the art would be motivated to select an ether or ester compound of a polyoxyalkylene for use in the method of Okada et al based on these teachings. Clearly the reagents that Applicant is claiming for packaging in a kit are well known in the art of measuring triglycerides with selectivity and claimed ratio of the surfactants does not appear to be outside the range suggested by the prior art as well and therefore the prior art renders obvious Applicant's invention as claimed.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657